Left Atrial Appendage Closure
State of the Art

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Atrial Fibrillation is one of the Most Important Causes of Death/Stroke

- >15% of all strokes are due to Atrial Fibrillation
- EU: > 3 mill. patients with AF
- > 1.5 million at high risk for stroke and require preventive therapy
Prevalence of Atrial Fibrillation

Framingham Study, Wolf, 1991
Atrial fibrillation is one of the most important causes of stroke
Especially in elder patients

% of strokes which are caused by AF

Framingham Study, Wolf, 1991
What is the stroke risk in atrial fibrillation?
Additional risk factors for an embolic stroke in atrial fibrillation

- Age >65
- Prior TIA / stroke
- Hypertension
- Diabetes
- Coronary heart disease
- Reduced LV function
- LAA flow velocity <20 cm/sec
- Spontaneous LAA echo contrast
What is the Annual Risk of Stroke? Nat. Registry of AF: CHADS$_2$

<table>
<thead>
<tr>
<th>CHADS Score</th>
<th># Pts n=1773</th>
<th># Strokes n=94</th>
<th>NRAF adjusted Stroke Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>2</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>17</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>23</td>
<td>4.0 (3.1-5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>25</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>19</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>6</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>
Randomized Clinical Trials of Coumadin in Atrial Fibrillation

Control

Warfarin

*p<0.05
Warfarin Net Clinical Benefit: 

Impact of Age

Net Clinical Benefit, Events Prevented per 100 Person – Years

Almost nobody can take Coumadin on the long term
- Any localized or general physical condition in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation
- Any personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation
  - Pregnancy
  - Hemorrhagic tendencies
  - Blood dyscrasias
  - Recent or contemplated surgery of central nervous system
  - Recent or contemplated surgery of the eye
  - Recent or contemplated traumatic surgery resulting in large open surfaces
  - Gastrointestinal bleeding
  - Genitourinary tract bleeding
  - Respiratory tract bleeding
  - Cerebrovascular hemorrhage

- Cerebral aneurysms
- Dissecting aorta
- Pericarditis
- Pericardial effusions
- Bacterial endocarditis
- Threatened abortion
- Eclampsia
- Preeclampsia
- Inadequate laboratory facilities
- Unsupervised patients
- Senility
- Alcoholism
- Psychosis
- Lack of patient cooperation
- Spinal puncture
- Other diagnostic procedures with potential for uncontrollable bleeding
- Therapeutic procedures with potential for uncontrollable bleeding
- Major regional anesthesia
- Lumbar block anesthesia
- Malignant hypertension
Effect of Intensity of Anticoagulation on Stroke and Bleeding in AF

Effect of Intensity of Anticoagulation on Stroke and Bleeding in AF

Anticoagulation Underuse

Only about 1/3 of all eligible patients are taking Coumadin

Stafford and Singer, Arch Int Med, 1996
Management of AF in Clinical Practice

Prescription of Anticoagulation

- **n = 23,657**
  - Medicare cohort, USA

- **n = 5,333**
  - EuroHeart survey

- **n = 11,379**
  - ATRIA cohort (managed care system, California, USA)
  - Go AS, et al. JAMA 2003;290:2685

![Pie charts showing prescription of anticoagulation](chart.png)
Anticoagulation Use in General Practice

Discontinuation

Other drugs?
Dabigatran - Major Bleeding

Significant, but small improvement

Dabigatran
Permanent Discontinuation

Dabigatran

- NNT 357
- 1.3 million US $ to prevent 1 stroke
All Anticoagulants

- Per definition
  - have to be given lifelong
  - have a bleeding risk
- Bleeding risk increases with age
- At some point Anticoagulants have to be stopped
- What does that mean in clinical practice?
  - You should avoid anticoagulants in elderly patients because of higher bleeding risk
  - You should avoid anticoagulants in younger patients because they would have to take it for a longer time period
Where do the thrombi arise?
Thrombus in the left atrial appendage
Thrombus in the LAA
Disappearing LAA Thrombus Resulting in Stroke

PLAATIO™ Device

ePTFE membrane

anchors

LA

LAA

Nitinol Cage
The first patient who underwent successful closure of the LAA

- Aug 30, 2001
- A.S., 72 y/o, male
- AF since 2 years
- Multiple contraindications for coumadin
- Very unstable INR
- CHADS score 3
First successful attempt of LAA closure

- Procedure time 85 min
- Complete seal
- No complications
- Coumadin off since 2001
- No neurological events
- Participated in other FIM trials
- Had his 80th birthday in Jan 2009
Watchman Device

- Nitinol frame
- PET membrane
- row of fixation barbs around the mid perimeter
- 21, 24, 27, 30, 33 mm
- CE mark
**WATCHMAN Device – Current vs Gen 4**

**Current**

- **160 µ PET Fabric**
- **Nitinol Frame**
- **Barbs**

- 21, 24, 27, 39, 33 mm (diameter)
- 10 cells
- Oversize 8 – 20%
- Fixation barbs (allow recapture)

**Gen 4**

- 22, 26, 31 mm (diameter)
- 18 cells
- Oversize 7 – 28%
- Bumper Stabilizer
- Prolapsed fixation barbs (allow multiple full recaptures and redeployments)

*Gen 4 is currently under clinical investigation*
Watchman Implantation

- LAA diameter in TEE 19 mm

- anatomy of LAA in TEE and fluoro
Watchman Implantation

<table>
<thead>
<tr>
<th>Maximum measured LAA ostium (mm)</th>
<th>Implant diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 - 19.5</td>
<td>21</td>
</tr>
<tr>
<td>20 - 22.9</td>
<td>24</td>
</tr>
<tr>
<td>23 - 25.9</td>
<td>27</td>
</tr>
<tr>
<td>26 – 28.9</td>
<td>30</td>
</tr>
<tr>
<td>29 – 31.9</td>
<td>33</td>
</tr>
</tbody>
</table>

- device selection according to measurements
- Implantation of 21mm Watchman Occluder
**Watchman Implantation**

- Check position
- Check device compression
- Check residual flow
- Tug test
- Release
Protect AF
(System for Embolic PROTECTion in Patients with Atrial Fibrillation)

- Multicenter
- Prospective randomized
- WATCHMAN vs coumadin 2:1
- Non-inferiority trial
- 800 pts (enrollment closed June 2008)
- > 900 patient-years
Patient Study Timeline

**Day 0**
- Post-Implant
- Randomize
- Control
- Day 0
  - Control patient takes Warfarin

**Day 2-14**
- Pre-implant interval
- Patient gets WATCHMAN
- Patient takes Warfarin
- Patient discontinues Warfarin / takes Clopidogrel
- Patient discontinues Clopidogrel

**Day 45**
- Day 45

**Day 180**
- Day 180

**Ongoing**
- Patient takes Warfarin
- Patient discontinues Warfarin / takes Clopidogrel
- Patient discontinues Clopidogrel
- Randomize
- Control patient takes Warfarin
- Day 0
In- & Exclusion

Major inclusion criteria

- Non valvular AF with Chads2 score ≥ 1
- No contraindications to coumadin
- No co-morbidities mandating chronic warfarin use other than AF

Major exclusion criteria

- LAA thrombus
- Large PFO with significant atrial septal aneurysm
- Mobile aortic atheroma
- Symptomatic carotid artery disease
PROTECT AF Trial Endpoints

• Primary Efficacy Endpoint
  • All stroke
  • Cardiovascular and unexplained death
  • Systemic embolization

• Primary Safety Endpoint
  • Device embolization requiring retrieval
  • Pericardial effusion requiring intervention
  • Cranial bleeds and gastrointestinal bleeds
  • Any bleed that requires ≥ 2uPRBC
Primary Efficacy Endpoint
Freedom from Stroke, Death, Systemic Embolization

LAA closure not inferior to anticoagulation
All Stroke

Events/100 patient years

Warfarin

P<0.05

LAA Closure

3.2

2.3

28%
Hemorrhagic Stroke

Warfarin: 1.6 events/100 patient years
LAA Closure: 0.1

P < 0.05

94% reduction
Mortality

Events/100 patient years

Warfarin: 4.8
LAA Closure: 3

P<0.05

38%
Safety

Freedom from device embolization, pericardial effusion, Severe bleeding

Control

Mostly pericardial effusion without sequelae

Mostly stroke and bleeding

Event-free probability

Days

0 365 730 1.095

0 0,8 0,9 1,0
## Performance Metrics

### PROTECT AF vs CAP

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF Early</th>
<th>PROTECT AF Late</th>
<th>CAP</th>
<th>p-value*</th>
<th>p-value±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Time</td>
<td>62 ± 34</td>
<td>67 ± 36</td>
<td>50 ± 21</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant Success</td>
<td>485/542 (89.5%)</td>
<td>239/271 (88.2%)</td>
<td>437/460 (95.0%)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>45-day Warfarin</td>
<td>414/478 (86.6%)</td>
<td>194/235 (82.6%)</td>
<td>352/371 (94.9%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinuation Among</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implanted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*From tests comparing the PROTECT AF cohort with CAP

±From tests for differences across three groups (early PROTECT AF, late PROTECT AF, and CAP)

- Improvements seen over time in PROTECT AF
  - Shorter implant time, higher implant success rate, higher warfarin discontinuation rate
- Trends confirmed in CAP
### Safety Event Rates

**PROTECT AF vs CAP**

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF Early</th>
<th>PROTECT AF Late</th>
<th>CAP</th>
<th>p-value*</th>
<th>p-value±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure/Device Related Safety Adverse Events within 7 Days</td>
<td>42/542 (7.7%)</td>
<td>27/271 (10.0%)</td>
<td>15/271 (5.5%)</td>
<td>17/460 (3.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serious Pericardial Effusions within 7 Days</td>
<td>27/542 (5.0%)</td>
<td>17/271 (6.3%)</td>
<td>10/271 (3.7%)</td>
<td>10/460 (2.2%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Procedure Related Stroke</td>
<td>5/542 (0.9%)</td>
<td>3/271 (1.1%)</td>
<td>2/271 (0.7%)</td>
<td>0/460 (0.0%)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

**Improvements seen over time for acute safety events**

**Fewer total procedure/device related events**

Kar et al. TCT 2010
ASAP Results

- 113 patients enrolled @ 4 centers in Europe
- Average CHADS$_2$ = 2.7
- Successful implantation in 105/113 pts (93%)
- Device or procedure related AE
  - 1 pericardial effusion - resolved
  - 1 device embolisation – retrieved
  - 1 pseudo-aneurysm – resolved
- Follow-up 7.9 mo
  - 43 patients @ 1 year
- 2 patients with device related thrombus @ 45 days and 3 mo TEE
  - Resolved w/ 2 mo SQ heparin
- 2 strokes during FU
Concept of PLAATO and Watchman

- To close the LAA like with a ball
Amplatzer Cardiac Plug ACP
Concept of Amplatzer Cardiac Plug ACP
M.I., female, 66 years

- Implantation
- Angiographic confirmation of correct position
M.I., female, 66 years
Final position

- 3D TEE: LA en-face view of the occluder
- 2D TEE 93°
New Approaches

- Endocardial
  - Occlutech
  - Coherex
  - Gore

- Epicardial
  - Epitec
  - AtriCure
  - SentreHeart
  - Aegis Medical
Coherex WaveCrest LAA Occlusion System

- Soft Nitinol frame
- Covered by polyurethane foam and e-PTFE
- 22, 27, 33 mm

- Special features
  - Separation of occlusion and anchoring
  - Occluder is completely re-positionable
Coherex WaveCrest

- “Roll-out” anchors
  - Separate structure from the occluder
  - Rolled out only when the occluder is in position
Coherex WaveCrest

- Anchoring is completely reversible
  - Anchor
  - Adjust / re-sheath
  - Re-anchor
- Detachment does not disrupt implant position
  - No torque transferred to implant during detachment
CSI 2011 – Catheter Interventions in Congenital & Structural Heart Disease

June 23 – 25, 2011 | Frankfurt, Germany

www.csi-congress.org
November 19, 2011 | Frankfurt, Germany

LAA 2011 – How to Close the Left Atrial Appendage

www.csi-laa.org
Take Home Messages

• Atrial fibrillation is a frequent cause of stroke
• Anticoagulation therapy is effective but difficult
• Thrombi originate from the left atrial appendage
• Catheter closure of the left atrial appendage is feasible, relatively safe and according to the PROTECT AF Trial equivalent to anticoagulation
• Two devices for LAA closure are available and there are more to come